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NEWS 25	Sep 16	Indexing added to some pre-1967 records in CA/CAPLUS
NEWS 26	Sep 16	CA Section Thesaurus available in CAPLUS and CA
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=> s GnRH chimera
L1             2 GNRH CHIMERA

=> dup remove l1
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L2             2 DUP REMOVE L1 (0 DUPLICATES REMOVED)

=> d l2 1-2 cbib abs

L2   ANSWER 1 OF 2  CAPLUS  COPYRIGHT 2002 ACS
1998:126357  Document No. 128:204067  Gonadotropin releasing
     hormone-leukotoxin chimeras and their use in vaccination.  Potter, Andrew
     A.; Manns, John G. (University of Saskatchewan, Can.).  PCT Int. Appl. WO
     9806848 A1 19980219, 128 pp.  DESIGNATED STATES: W:  AL, AM, AT, AU, AZ,
     BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU,
     IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK,
     MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT,
     UA, UG, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ,
     CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML,
     MR, NE, NL, PT, SE, SN, TD, TG.  (English).  CODEN: PIXXD2.  APPLICATION:
     WO 1997-CA559 19970808.  PRIORITY: US 1996-694865 19960809.
AB   New immunol. carrier systems, DNA encoding the same, and the use of these
     systems, are disclosed.  The carrier systems include chimeric proteins
     which include a leukotoxin polypeptide fused to one or more selected
     gonadotropin releasing hormone (GnRH) multimers which comprise at least
     one repeating GnRH decapeptide sequence, or at least one repeating unit of
     a sequence corresponding to at least one epitope of a selected GnRH mol.
     Under the invention, the selected GnRH sequences may all be the same, or
     may correspond to different derivs., analogs, variants or epitopes of GnRH
     so long as the GnRH sequences are capable of eliciting an immune response.
     The leukotoxin functions to increase the immunogenicity of the GnRH
     multimers fused thereto.  The chimeric proteins may be used to reduce
     incidence of mammary tumors.  Truncated, non-cytotoxic Pasteurella
     haemolytica leukotoxins fused to 4 or 8 copies of mammalian GnRH were
     prepd. with recombinant Escherichia coli.  Immunogenicity was increased by
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decreasing the size of the leukotoxin component and by increasing the no. of GnRH in the fusion protein. The leukotoxin-**GnRH chimeras** were effective in immunocastration of boars.

L2 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2002 ACS
1996:639621 Document No. 126:1325 GnRH-toxin chimera as chemosterilants: Synthesis and conjugation of GnRH analogs to truncated bacterial toxins. Rusiecki, V. K.; Mohn, K. L.; Yang, Y. T.; Marsilio, F.; O'Keefe, D.; Yamazaki, S.; Lee, C.; Childs, G. V.; Hickey, G. J.; Tolman, R. L. (Department Synthetic Chemical Research, Merck Research Laboratories, Rahway, NJ, 07065, USA). Peptides 1994, Proceedings of the European Peptide Symposium, 23rd, Braga, Port., Sept. 4-10, 1994, Meeting Date 1994, 765-766. Editor(s): Maia, Hernani L. S. ESCOM: Leiden, Neth. (English) 1995. CODEN: 63MBAO.
AB The authors have demonstrated that chem. defined conjugates of GnRH peptides and Pseudomonas exotoxin can be prepd. These materials all bound the targeted GnRH receptor and retained significant ADP ribosylase activity. Surprisingly, these constructs lacked marked cytotoxicity to gonadotrophs in vitro and in vivo. Electron microscopy with peroxidase labeled anti-PE antibody demonstrated aggregation of the **GnRH chimera** on the gonadotroph surface with no significant endocytosis.

=> s GnRH fusion protein
L3 8 GNRH FUSION PROTEIN

=> dup remove l3
PROCESSING COMPLETED FOR L3
L4 4 DUP REMOVE L3 (4 DUPLICATES REMOVED)

=> d l4 1-4 cbib abs

L4 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2002 ACS
2000:611884 Document No. 133:203826 Gonadotropin releasing hormone-bovine herpes virus-1 antigen fusion protein for inducing a double immune response in vertebrate, and vaccine use. Campos, Manuel; Dartsky, Becky Ann; Martino, Serge Rene; Yule, Terecita D. (Pfizer Products Inc., USA). Jpn. Kokai Tokkyo Koho JP 2000236887 A2 20000905, 81 pp. (Japanese). CODEN: JKXXAF. APPLICATION: JP 2000-39532 20000217. PRIORITY: US 1999-PV120454 19990217.
AB A fusion protein for inducing a double immune response in vertebrate, comprising a vertebrate endogenous peptide or its fragment and pathogen derived antigen or its homolog, is disclosed. The activity of the peptide is to be inhibited in the vertebrate. Expression vectors for gonadotropin releasing hormone (**GnRH**) **fusion protein** with bovine herpes virus-1 antigen (BHV-1 gD) were constructed. GnRH/BHV-1 gD fusion protein was expressed in E. coli and via baculovirus infection in Sf21 insect cells. Mice injected with the vaccine composed of GnRH/BHV-1 gD fusion protein showed lower testosterone level and redn. in size of reproductive organs.

L4 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2002 ACS
1999:783957 Document No. 132:19228 Methods for suppressing reproductive behavior in animals using compositions containing GnRH immunogens, analogs, and antibodies. Robbins, Sarah C. (Biostar Inc., Can.). PCT Int. Appl. WO 9962545 A2 19991209, 88 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL,

PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-CA493 19990528. PRIORITY: US 1998-88024 19980604; US 1999-306689 19990506.

AB Methods for achieving suppression of reproductive behavior and/or fertility in a vertebrate subject are disclosed. The methods use compns., administered prior to puberty, contg. GnRH immunogens, GnRH analogs such as GnRH agonists and antagonists, or GnRH antibodies. The methods are useful for the prolonged suppression of testicular function in males and ovarian function in females. The GnRH immunogen of the invention is a GnRH multimer comprising the general formula (GnRH-X-GnRH)y wherein: GnRH is a GnRH immunogen; X is one or more mols. selected from the group consisting of a peptide linkage, an amino acid spacer group, a carrier mol. and [GnRH]n, where n is an integer greater than or equal to 1; and y is an integer greater than or equal to 1. The carrier mol. is specifically a leukotoxin polypeptide. The compn. can further contain an immunol. adjuvant. The vertebrate of the invention is selected from the group consisting of a feline subject, a canine subject, an equine subject and a cervine subject.

L4 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2002 ACS

1998:548554 Document No. 129:160627 Immunization against endogenous gonadotropin-releasing hormone. Harland, Richard; Manns, John G.; Acres, Stephen D. (Biostar Inc., Can.). PCT Int. Appl. WO 9834639 A1 19980813, 61 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1998-CA59 19980204. PRIORITY: US 1997-36883 19970205.

AB A method is described for immunoneutralization of endogenous hormone mols. in mammalian subjects, wherein an immunogen is administered via injection to the ear. The method was used to induce an immune response against a **GnRH fusion protein** in cattle and pigs.

L4 ANSWER 4 OF 4 MEDLINE DUPLICATE 1

94191098 Document Number: 94191098. PubMed ID: 8142546. Testosterone effects on spermatogenesis in the gonadotropin-releasing hormone-immunized rat. McLachlan R I; Wreford N G; Tsonis C; De Kretser D M; Robertson D M. (Prince Henry's Institute of Medical Research, Monash University, Clayton, Victoria, Australia.) BIOLOGY OF REPRODUCTION, (1994 Feb) 50 (2) 271-80. Journal code: 0207224. ISSN: 0006-3363. Pub. country: United States. Language: English.

AB Active immunization of adult rats with a **GnRH fusion protein** was used to inhibit gonadotropin secretion and to establish an in vivo model for studying the hormonal control of spermatogenesis. The model was characterized in terms of the efficacy of the immunogen as well as the time course and nature of the immunological and biological responses. To study the reinitiation of spermatogenesis, testosterone (T) was chosen for this initial study as it is known to restore spermatogenesis in gonadotropin-deficient rats. Adult Sprague-Dawley rats were actively immunized with a proprietory GnRH immunogen (BA-11, 100 micrograms s.c.) every 4 wk. After 12 wk, 58% of animals showed markedly suppressed testicular size, as assessed by scrotal palpation, and were classed as responders. Serum LH, FSH, and T as well as the testicular elongated spermatid count (ESC) and epididymal sperm were undetectable in responding animals. Marked reductions in testicular (29% of control), prostatic (8% of control), and epididymal (32% of control) weights were seen. Spermatogenesis was severely disrupted with no evidence of progression beyond round spermatids. To study the action of T in GnRH-immunized animals, T (defined by lengths of s.c. silastic implant, T3-T24 cm) was given to responding animals. Animals were killed 2, 8, and

12 wk after T24 administration. In response to T24, serum T levels increased to 4 times control levels, serum FSH levels were restored to 65% of control levels by 2 wk, and serum LH remained undetectable. Testicular weight increased to 80% of control levels at 12 wk ($p < 0.05$ vs. control). Epididymal and prostatic weights were normalized by T. ESC increased to 82% of control values at 12 wk (110 +/- 10 vs. control 134 +/- 8 million/testis, $p = 0.001$). Spermatogenesis was histologically normal after 8 wk of T24 treatment. To study the time course and dose response of T action, animals were immunized with another GnRH immunogen (BA-17), which yielded an 87% response rate at 12 wk. Testicular weight increased by Day 5 of T24 treatment, and a clear dose-response effect was apparent. The restoration of ESC was delayed compared to that of testicular weight (no restoration at 2 wk) and required > or = T6 treatment. Rats immunized for 20 wk and then given T24 treatment showed a similar pattern of restoration in testicular weight and ESC. Serum FSH was normalized by Day 2 of T treatment by doses > or = 3 cm.(ABSTRACT TRUNCATED AT 400 WORDS)

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=> s LHRH
L5        37447 LHRH

=> s l5 and fusion
L6          162 L5 AND FUSION

=> s l6 and T cell epitope
   3 FILES SEARCHED...
L7            6 L6 AND T CELL EPITOPE

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L8            2 DUP REMOVE L7 (4 DUPLICATES REMOVED)

=> d l8 1-2 cbib abs

L8   ANSWER 1 OF 2     MEDLINE                                  DUPLICATE 1
2001529780  Document Number: 21460587.    PubMed ID: 11576221.   Identification
     of canine helper T-cell epitopes from the
     fusion protein of canine distemper virus. Ghosh S; Walker J;
     Jackson D C. (Cooperative Research Center for Vaccine Technology,
     Department of Microbiology and Immunology, The University of Melbourne,
     Parkville, Victoria, Australia. ) IMMUNOLOGY, (2001 Sep) 104 (1) 58-66.
     Journal code: 0374672. ISSN: 0019-2805. Pub. country: England: United
     Kingdom. Language: English.
AB   The fusion protein of canine distemper virus (CDV-F), a 662
     amino-acid envelope protein, was used as the target molecule for
     identification of canine T helper (Th) epitopes. A library of 94 peptides,
     each 17 residues in length overlapping by 10 residues and covering the
     entire sequence of CDV-F, was screened using a lymphocyte proliferation
     assay with peripheral blood mononuclear cells (PBMC) obtained from dogs
     inoculated with canine distemper virus (CDV) vaccine. Initially we
     observed low and inconsistent proliferation of PBMC in response to these
     peptides, even when using cells obtained from dogs that had received
     multiple doses of CDV. Subsequently, the use of expanded cell populations
     derived by in vitro stimulation of canine PBMC with pools of peptides
     allowed the identification of a number of putative canine Th-epitopes
     within the protein sequence of CDV-F. There were two major clusters of
     Th-epitopes identified close to the cleavage site of the F0 fusion
     protein, while some others were scattered in both the F1 and F2 fragments
     of the protein. Some of these peptides, in particular peptide 35 (p35),
     were stimulatory in dogs of different breeds and ages. The identification
     of such promiscuous canine Th-epitopes encouraged us to assemble p35 in
     tandem with luteinising hormone releasing hormone (LHRH) a 10
     amino-acid residue synthetic peptide representing a B-cell epitope which
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alone induces no antibody in dogs. The totally synthetic immunogen was able to induce the production of very high titres of antibodies against **LHRH** in all dogs tested. These results indicate that p35 could be an ideal candidate for use as a Th-epitope for use in outbred dogs.

L8 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2002 ACS
1995:340887 Document No. 122:131007 Immunogenic **LHRH** peptide constructs and synthetic universal immune stimulators for vaccines. Ladd, Anna E.; Wang, Chang Yi; Zamb, Timothy (USA). PCT Int. Appl. WO 9425060 A1 19941110, 217 pp. DESIGNATED STATES: W: AU, CA, FI, JP, KR, NO, US; RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1994-US4832 19940428. PRIORITY: US 1993-57166 19930427; US 1994-229275 19940414.
AB This invention relates to immunogenic LH releasing hormone (**LHRH**) peptides that lead to suppression of **LHRH** activity in males or females. When male rats are immunized with these peptides, serum testosterone drops and androgen-dependent organs atrophy significantly. These peptides are useful for inducing infertility and for treating prostatic hyperplasia, androgen-dependent carcinoma, prostatic carcinoma and testicular carcinoma in males. In females, the peptides are useful for treating endometriosis, benign uterine tumors, recurrent functional ovarian cysts and (severe) premenstrual syndrome as well as prevention or treatment of estrogen-dependent breast cancer. The subject peptides contain a helper **T cell epitope** and have **LHRH** at the C terminus. The helper **T cell epitope** aids in stimulating the immune response against **LHRH**. The peptides, optionally contain an invasin domain which acts as a general immune stimulator. In another aspect this invention relates to immunogenic synthetic peptides having an invasin domain, a helper **T cell epitope** and a peptide hapten and methods of using these peptides to treat disease or provide protective immunity. The peptide haptens of the invention include **LHRH**, amylin, gastrin, gastrin releasing peptide, IgE CH4 peptide, Chlamydia MOMP peptides, HIV V3 peptides and Plasmodium berghei.

=> s fusion protein
L9 133240 FUSION PROTEIN

=> s l9 and tetanus toxoid
L10 131 L9 AND TETANUS TOXOID

=> s l10 and malaria plasmodium falciparum CSP protein
L11 0 L10 AND MALARIA PLASMODIUM FALCIPARUM CSP PROTEIN

=> s l10 and DT
L12 9 L10 AND DT

=> dup remove l12
PROCESSING COMPLETED FOR L12
L13 5 DUP REMOVE L12 (4 DUPLICATES REMOVED)

=> d l13 1-5 cbib abs

L13 ANSWER 1 OF 5 SCISEARCH COPYRIGHT 2002 ISI (R)
2001:615410 The Genuine Article (R) Number: 456NZ. Lipophilic quaternary ammonium salt acts as a mucosal adjuvant when co-administered by the nasal route with vaccine antigens. Klinguer C; Beck A; De-Lys P; Bussat M C; Blaecke A; Derouet F; Bonnefoy J Y; Nguyen T N; Corvaia N; Velin D (Reprint). Bio Merieux Pierre Fabre, Ctr Immunol Pierre Fabre, 5 Ave Napoleon 3, BP 497, St Julien En Genevois, France (Reprint); Bio Merieux Pierre Fabre, Ctr Immunol Pierre Fabre, St Julien En Genevois, France. VACCINE (20 JUL 2001) Vol. 19, No. 30, pp. 4236-4244. Publisher: ELSEVIER

SCI LTD. THE BOULEVARD, LANGFORD LANE, KIDLINGTON, OXFORD OX5 1GB, OXON, ENGLAND. ISSN: 0264-410X. Pub. country: France. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Nasal administration of vaccines is an attractive approach which offers several significant advantages over traditional intramuscular vaccine delivery. These advantages include easier administration and induction of immune responses in the mucosal secretions of the body. In this study we describe a new potent nasal adjuvant, dimethyldioctadecylammonium bromide (DDA), that induces both mucosal and systemic immune responses when co-administered with diphtheria toxoid (**DT**), **tetanus toxoid** (TT) and BBG2Na antigens. In particular, we show that the nasal delivery of recombinant fragment (BBG2Na) of the G protein of respiratory syncytial virus (RSV) mixed with DDA induces both local and systemic anti-RSV immune responses and protects against viral challenge. Furthermore, we provide evidence that the DDA + BBG2Na vaccine does not induce lung immunopathology upon subsequent RSV challenge.

L13 ANSWER 2 OF 5 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

2000176408 EMBASE Differential recognition of a BCR/ABL peptide by lymphocytes from normal donors and chronic myeloid leukemia patients.
Bertazzoli C.; Marchesi E.; Passoni L.; Barni R.; Ravagnani F.; Lombardo C.; Corneo G.M.; Pioltelli P.; Pogliani E.; Gambacorti-Passerini C.. C. Gambacorti-Passerini, Istituto Nazionale Tumori, Oncogenic Fusion Proteins Unit, Department of Experimental Oncology, Via Venezian 1, 20133 Milan, Italy. Gambacorti@istitutotumori.mi.it. Clinical Cancer Research 6/5 (1931-1935) 2000.
Refs: 20.
ISSN: 1078-0432. CODEN: CCREF4. Pub. Country: United States. Language: English. Summary Language: English.

AB The BCR/ABL oncogenic **fusion protein** transforms normal bone marrow stem cells into neoplastic cells. It has been shown that peptides derived from the junctional region of this oncogenic **fusion protein** can be recognized by human T-lymphocytes obtained from normal donors. In this study, we investigated the immunogenicity in patients with chronic myeloid leukemia (CML) of a 17 mer b3/a2 Bcr/abl peptide (B/A1), which was shown to induce proliferative responses in lymphocytes from normal donors. A total of 56 CML patients in chronic phase were studied. Twenty-two patients were studied at diagnosis without any treatment (group I). Fourteen patients were receiving IFN (group II), 14 patients were being treated with hydroxyurea (group III), and 6 patients were on different regimens (group IV). Patients were initially assessed for general immunological competence using both in vivo and in vitro assays. Patients were also selected for the expression of HLA-DR0401, the HLA specificity known to present peptide B/A1 to CD4 lymphocytes. With the exception of the six patients in group IV, the results of all these assays (in vitro phytohemagglutinin/**tetanus toxoid** responses, in vivo skin reaction to ubiquitous antigens) in CML patients did not significantly differ from those obtained in normal donors, thus excluding the presence of generalized immunosuppression. Eight patients with HLA-DR0401 and a b3/a2 type of fusion were identified and further studied. In these eight patients dendritic cells were obtained from adherent peripheral blood mononuclear cells and used to stimulate CD4 lymphocytes. No patient developed a specific response to the bcr/abl peptide, although patients' lymphocytes proliferated in response to a promiscuous **tetanus toxoid** peptide in all but one case. In contrast, response to the bcr/abl peptide was observed in seven of eight HLA-DR0401 healthy donors tested. These data suggest that immunocompetent, HLA-DR0401+ CML patients are unable to respond to peptide B/A1, at difference from healthy donors. The implication of these results for the immunotherapy of CML is discussed.

L13 ANSWER 3 OF 5 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

2001053638 EMBASE Passive immunization for the prevention of otitis media.
Englund J.A.; Glezen W.P.. J.A. Englund, Department of Pediatrics, University of Chicago Hospitals, Chicago, IL 60637, United States. Vaccine 19/SUPPL. 1 (S116-S121) 8 Dec 2000.
Refs: 44.
ISSN: 0264-410X. CODEN: VACCDE.
Publisher Ident.: S 0264-410X(00)00289-9. Pub. Country: United Kingdom.
Language: English. Summary Language: English.

AB The safety and protective efficacy of exogenously-administered immunoglobulin for the prevention of otitis media has been demonstrated in the clinical trials of the human-derived polyclonal immune globulin used to prevent Haemophilus influenzae type b disease and respiratory syncytial virus infection in high risk neonates and young children. However, this form of therapy is expensive, difficult to administer due to the requirements of slow intravenous infusion or relatively large volumes given intramuscularly, and associated with side effects related to the volume and nature of the immunoglobulin preparation. In contrast, RSV-specific monoclonal antibody has not been as successful as human-derived immunoglobulin in preventing otitis media in high risk infants. The administration of monoclonal-antibody for the prevention of otitis media will be difficult, potentially due to the need for antibody to multiple epitopes of the viral and bacterial pathogens which could be targets. The use of maternal antibody to provide passive immunity to young infants at a time when they are most vulnerable to severe sequelae of infection can also be considered. We have studied maternal immunization using either a 23-valent pneumococcal polysaccharide vaccine or a conjugate H. influenzae type b (Hib) vaccine. Significant levels of maternally-derived Hib or pneumococcal antibody were transferred from the mother to the infant at the time of birth and persisting, for some antigens, through 2 months of age. The use of maternal immunization to prevent otitis media and other respiratory complications remains to be studied, but results of these small clinical trials indicate further clinical investigation is warranted. .COPYRGT. 2000 Elsevier Science Ltd.

L13 ANSWER 4 OF 5 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
1998265170 EMBASE Maternal immunization against viral disease. Englund J.; Glezen W.P.; Piedra P.A.. J. Englund, Microbiol./Immunology/Pediatr. Dept., Baylor College of Medicine, Houston, TX 77030, United States. jenglund@bcm.tmc.edu. Vaccine 16/14-15 (1456-1463) 1998.
Refs: 75.
ISSN: 0264-410X. CODEN: VACCDE.
Publisher Ident.: S 0264-410X(98)00108-X. Pub. Country: United Kingdom.
Language: English. Summary Language: English.

AB The protective effect of maternal antibody against many vital diseases has been recognized. The use of maternal immunization has been considered as a means to augment this protection in the young infant against disease. Advantages of maternal immunization include the fact that young infants are most susceptible to infections but least responsive to vaccines, that pregnant women are accessible to medical care and respond well to vaccines, that IgG antibodies cross the placenta well during the third trimester, and that immunization of the pregnant woman has the potential to benefit both the mother and the infant. Disadvantages include the potential inhibition of an infant's response to active immunization or natural infection and liability issues with pharmaceutical companies and physicians. Immunization of pregnant women with viral vaccines for poliovirus, influenza viruses, and rubella has been described and maternal vaccination with these vaccines has been found to be safe for both the mother and the fetus. An open-label study of post- partum women immunized with the purified **fusion protein** of RSV (PFP-2, Wyeth-Lederle Pediatrics and Vaccines, Inc., Pearl River, NY) demonstrated that the vaccine was non-reactogenic and immunogenic; RSV-specific antibody was detected in breast milk. Immunization of pregnant women with purified protein or subunit vaccines could be considered against neonatal viral

pathogens, such as respiratory syncytial virus, parainfluenza viruses, herpes group viruses, and human immunodeficiency virus. Further studies are needed to define the safety and efficacy of maternal immunization.

L13 ANSWER 5 OF 5 MEDLINE DUPLICATE 1
1998347286 Document Number: 98347286. PubMed ID: 9682364. Investigation into suitable carrier molecules for use in an anti-gonadotrophin releasing hormone vaccine. Ferro V A; Stimson W H. (University of Strathclyde, Department of Immunology, Glasgow, Scotland.) VACCINE, (1998 Jul) 16 (11-12) 1095-102. Journal code: 8406899. ISSN: 0264-410X. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Gonadal function can be controlled through immunoneutralisation of gonadotrophin releasing hormone (GnRH), with an analogue, GnRH-glycys, linked to a carrier molecule and an appropriate adjuvant. In this study, four different types of carrier molecule were investigated: (a) single and branched amino acid polymers--[poly-(D-glu, D-lys) and poly-(phe, glu)-poly(DL-ala)-poly(lys)]; (b) bacterial toxoids--diphtheria (**DT**) and tetanus (TT); (c) synthetic T-helper epitopes--derived from malarial circumsporozite protein (CS) and measles virus **fusion protein** (MVF); and (d) thyroglobulin (Thy)--a large protein. The effect of non-ionic surfactant vesicles (NISV) and an aluminum hydroxide based adjuvant (alum), was also examined. Although good antibody responses were achieved with GnRH-glycys-**DT**, GnRH-glycys-TT and GnRH-glycys-Thy, adsorbed onto alum and the dimerised synthetic T-helper epitope constructs, incorporated into NISV, a critical antibody titre was necessary to result in morphological changes in the gonads and complete suppression of spermatogenesis. This was only achieved with **tetanus toxoid** and the dimerised T-helper epitopes.

=> s l6 and CSF protein
L14 0 L6 AND CSF PROTEIN

=> s l6 and T cell epitope
3 FILES SEARCHED...
L15 6 L6 AND T CELL EPITOPE

=> dup remove l15
PROCESSING COMPLETED FOR L15
L16 2 DUP REMOVE L15 (4 DUPLICATES REMOVED)

=> d l16 1-2 cbib abs

L16 ANSWER 1 OF 2 MEDLINE DUPLICATE 1
2001529780 Document Number: 21460587. PubMed ID: 11576221. Identification of canine helper **T-cell epitopes** from the **fusion** protein of canine distemper virus. Ghosh S; Walker J; Jackson D C. (Cooperative Research Center for Vaccine Technology, Department of Microbiology and Immunology, The University of Melbourne, Parkville, Victoria, Australia.) IMMUNOLOGY, (2001 Sep) 104 (1) 58-66. Journal code: 0374672. ISSN: 0019-2805. Pub. country: England: United Kingdom. Language: English.

AB The **fusion** protein of canine distemper virus (CDV-F), a 662 amino-acid envelope protein, was used as the target molecule for identification of canine T helper (Th) epitopes. A library of 94 peptides, each 17 residues in length overlapping by 10 residues and covering the entire sequence of CDV-F, was screened using a lymphocyte proliferation assay with peripheral blood mononuclear cells (PBMC) obtained from dogs inoculated with canine distemper virus (CDV) vaccine. Initially we observed low and inconsistent proliferation of PBMC in response to these peptides, even when using cells obtained from dogs that had received multiple doses of CDV. Subsequently, the use of expanded cell populations

derived by in vitro stimulation of canine PBMC with pools of peptides allowed the identification of a number of putative canine Th-epitopes within the protein sequence of CDV-F. There were two major clusters of Th-epitopes identified close to the cleavage site of the F0 **fusion** protein, while some others were scattered in both the F1 and F2 fragments of the protein. Some of these peptides, in particular peptide 35 (p35), were stimulatory in dogs of different breeds and ages. The identification of such promiscuous canine Th-epitopes encouraged us to assemble p35 in tandem with luteinising hormone releasing hormone (**LHRH**) a 10 amino-acid residue synthetic peptide representing a B-cell epitope which alone induces no antibody in dogs. The totally synthetic immunogen was able to induce the production of very high titres of antibodies against **LHRH** in all dogs tested. These results indicate that p35 could be an ideal candidate for use as a Th-epitope for use in outbred dogs.

L16 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2002 ACS
1995:340887 Document No. 122:131007 Immunogenic **LHRH** peptide constructs and synthetic universal immune stimulators for vaccines. Ladd, Anna E.; Wang, Chang Yi; Zamb, Timothy (USA). PCT Int. Appl. WO 9425060 A1 19941110, 217 pp. DESIGNATED STATES: W: AU, CA, FI, JP, KR, NO, US; RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1994-US4832 19940428. PRIORITY: US 1993-57166 19930427; US 1994-229275 19940414.

AB This invention relates to immunogenic LH releasing hormone (**LHRH**) peptides that lead to suppression of **LHRH** activity in males or females. When male rats are immunized with these peptides, serum testosterone drops and androgen-dependent organs atrophy significantly. These peptides are useful for inducing infertility and for treating prostatic hyperplasia, androgen-dependent carcinoma, prostatic carcinoma and testicular carcinoma in males. In females, the peptides are useful for treating endometriosis, benign uterine tumors, recurrent functional ovarian cysts and (severe) premenstrual syndrome as well as prevention or treatment of estrogen-dependent breast cancer. The subject peptides contain a helper **T cell epitope** and have **LHRH** at the C terminus. The helper **T cell epitope** aids in stimulating the immune response against **LHRH**. The peptides, optionally contain an invasin domain which acts as a general immune stimulator. In another aspect this invention relates to immunogenic synthetic peptides having an invasin domain, a helper **T cell epitope** and a peptide hapten and methods of using these peptides to treat disease or provide protective immunity. The peptide haptens of the invention include **LHRH**, amylin, gastrin, gastrin releasing peptide, IgE CH4 peptide, Chlamydia MOMP peptides, HIV V3 peptides and Plasmodium berghei.

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=> s l6 and "CSP protein"
L17             0 L6 AND "CSP PROTEIN"

=> s l6 and "MSP-F"
L18             0 L6 AND "MSP-F"

=> s l6 and T cell epitope
   3 FILES SEARCHED...
L19             6 L6 AND T CELL EPITOPE

=> s l19 and measule virus
L20             0 L19 AND MEASULE VIRUS

=> s l19 and measles virus
L21             1 L19 AND MEASLES VIRUS

=> d l21 cbib abs
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L21 ANSWER 1 OF 1 SCISEARCH COPYRIGHT 2002 ISI (R)
2001:829967 The Genuine Article (R) Number: 481CA. Identification of canine helper **T-cell epitopes** from the **fusion** protein of canine distemper virus. Ghosh S; Walker J; Jackson D C (Reprint). Univ Melbourne, Dept Microbiol & Immunol, Cooperat Res Ctr Vaccine Technol, Parkville, Vic 3052, Australia (Reprint); CSL Ltd, Anim Hlth, Parkville, Vic, Australia. IMMUNOLOGY (SEP 2001) Vol. 104, No. 1, pp. 58-66. Publisher: BLACKWELL SCIENCE LTD. P O BOX 88, OSNEY MEAD, OXFORD OX2 0NE, OXON, ENGLAND. ISSN: 0019-2805. Pub. country: Australia. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The **fusion** protein of canine distemper virus (CDV-F), a 662 amino-acid envelope protein, was used as the target molecule for identification of canine T helper (Th) epitopes. A library of 94 peptides, each 17 residues in length overlapping by 10 residues and covering the entire sequence of CDV-F, was screened using a lymphocyte proliferation assay with peripheral blood mononuclear cells (PBMC) obtained from dogs inoculated with canine distemper virus (CDV) vaccine. Initially we observed low and inconsistent proliferation of PBMC in response to these peptides, even when using cells obtained from dogs that had received multiple doses of CDV. Subsequently, the use of expanded cell populations derived by in vitro stimulation of canine PBMC with pools of peptides allowed the identification of a number of putative canine Th-epitopes within the protein sequence of CDV-F. There were two major clusters of Th-epitopes identified close to the cleavage site of the F0 **fusion** protein, while some others were scattered in both the F1 and F2 fragments of the protein. Some of these peptides, in particular peptide 35 (p35), were stimulatory in dogs of different breeds and ages. The identification of such promiscuous canine Th-epitopes encouraged us to assemble p35 in tandem with luteinising hormone releasing hormone (**LHRH**) a 10 amino-acid residue synthetic peptide representing a B-cell epitope which alone induces no antibody in dogs, The totally synthetic immunogen was able to induce the production of very high titres of antibodies against **LHRH** in all dogs tested. These results indicate that p35 could be an ideal candidate for use as a Th-epitope for use in outbred dogs.

=> s l6 and linker
L22 2 L6 AND LINKER

=> dup remove l22
PROCESSING COMPLETED FOR L22
L23 2 DUP REMOVE L22 (0 DUPLICATES REMOVED)

=> d l23 1-2 cbib abs

L23 ANSWER 1 OF 2 MEDLINE
2000237076 Document Number: 20237076. PubMed ID: 10772899. Identification of an upstream promoter in the human gonadotropin-releasing hormone receptor gene. Ngan E S; Leung P C; Chow B K. (Department of Zoology, University of Hong Kong, Pokfulam Road, Hong Kong, SAR, China.) BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (2000 Apr 21) 270 (3) 766-72. Journal code: 0372516. ISSN: 0006-291X. Pub. country: United States. Language: English.

AB Analysis of the human gonadotropin-releasing hormone receptor (hGnRHR) gene 5' flanking region revealed the presence of multiple TATA, CCAAT, and transcription start sites. In addition, at least three different transcripts (5.0, 2.5, and 1.5 kb) were detected by Northern blot analysis. Taken together, these data indicated the existence of multiple promoter elements in the hGnRHR gene, and these promoters are responsible for the multiplicity of regulation of human reproductive functions. In this report, by progressive 5' and 3' deletion (-2197 to -1351, relative

to the ATG) and NotI **linker** scanning mutagenesis coupled to transient transfection into the mouse gonadotrope-derived alphaT3-1 cell, a distal promoter element was identified at -1705/-1674. The promoter was located immediately 5' to a previously identified CAP site at -1673 in human pituitary and it drove a 17.6- +/- 1.0-fold increase in reporter gene activity. Within the promoter, a pyrimidine-rich initiator element (Inr) (-1682) and a CCAAT box (-1702) were found and mutation of these elements abrogated both protein bindings and promoter activities. By 1- and 2-D SouthWestern blot assays, multiple nuclear factors (40 to 54 kDa) were found to interact specifically with this promoter element. These nuclear factors were also present in other cells, including COS-7, JEG-3, and SKOV-3 cells, and these findings were consistent with functional studies which showed that the promoter is also active in these cells. Copyright 2000 Academic Press.

L23 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2002 ACS
1997:85595 Document No. 126:167481 Recombinant production and purification of peptides using carbonic anhydrase-peptide **fusion** products and affinity chromatography. Coolidge, Thomas R.; Wagner, Fred; Van, Heeke Gino; Schuster, Sheldon M.; Stout, Jay; Wylie, Dwane E. (Bionebraska, Inc., USA). U.S. US 5595887 A 19970121, 27 pp. (English). CODEN: USXXAM. APPLICATION: US 1990-552810 19900716.
AB Methods are presented for producing and purifying a variable **fusion** polypeptide which can be purified by affinity chromatog. with the binding protein partner. The variable **fusion** polypeptide construct has tandem coupled segments contg. one or more copies of a desired peptide linked to carbonic anhydrase as the purifn. binding protein. In the methods, the **fusion** protein is expressed in a recombinant host using a recombinant vector contg. a gene encoding the **fusion** polypeptide. Then the expressed **fusion** polypeptide is purified by immobilized reversible inhibitor affinity chromatog. Finally, the purified **fusion** polypeptide is cleaved from the desired peptides by chem. or enzymic means and the desired peptides purified with affinity chromatog.

=> s peptide linker
L24 822 PEPTIDE LINKER

=> s l24 and "GPSL"
L25 0 L24 AND "GPSL"

=> s l24 and "Gly Pro Ser Leu"
L26 0 L24 AND "GLY PRO SER LEU"

=> s (grimes s?/au or michaeli d?/au or stevens v?/au)
L27 2869 (GRIMES S?/AU OR MICHAELI D?/AU OR STEVENS V?/AU)

=> s l27 and GnRH
L28 26 L27 AND GNRH

=> dup remove l28
PROCESSING COMPLETED FOR L28
L29 14 DUP REMOVE L28 (12 DUPLICATES REMOVED)

=> d l29 1-14 cbib abs

L29 ANSWER 1 OF 14 CAPLUS COPYRIGHT 2002 ACS
2001:833350 Document No. 135:370623 Chimeric peptide immunogens.
Grimes, Stephen; Michaeli, Dov; Stevens, Vernon C. (Aphton Corporation, USA). PCT Int. Appl. WO 2001085763 A2 20011115, 43 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES,

FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US14363 20010504. PRIORITY: US 2000-PV202328 20000505.

AB Chimeric peptide epitopes can serve as effective immunogens against hormones and other small peptides or proteins. Thus, immunogenic peptides are selected from promiscuous Th epitopes and synthesized together with self antigenic peptide sequences fused with or without end to end spacer peptide interconnections. A peptide sequence which may be of the gonadotropin releasing hormone is linked with an immunogenic peptide sequence selected from a promiscuous Th-epitope of measles virus protein F, tetanus toxoid, or malaria protein CSP. Compns. of the chimeric immunogen are found effective in eliciting high and specific anti-**GnRH** antibody titers.

L29 ANSWER 2 OF 14 CAPLUS COPYRIGHT 2002 ACS

2001:472459 Document No. 135:66189 A stable immunogenic composition for frozen storage containing protein carriers. **Grimes, Stephen;** Blackburn, Peter (Aphton Corporation, USA). PCT Int. Appl. WO 2001045670 A2 20010628, 48 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US35248 20001222. PRIORITY: US 1999-PV173022 19991223.

AB An injectable vaccine compn. comprising an immunogenic conjugate in an emulsion contg. advantageous oily vehicles is disclosed as suitable for frozen storage; moreover, a water-in-oil emulsion compn. is found to enhance immunogenicity after storage at about -18.degree.. For example, an aq. phase droplets of an anti-gastrin immunogenic emulsion (e.g., human gastrin 17(1-9)Ser 9-diphtheria toxoid conjugate) were stable at -70.degree., -18.degree., and 4.degree., but less stable at 25.degree.. The conjugate purity was most stable at -70.degree. and -18.degree., less stable at 4.degree. and much less stable at 25.degree.. The behavior in the release assay was not altered by storage at any four select temps. The immunogenicity response was unaffected by storage at 4.degree.. Storage at -18.degree. increased immunogenicity. The finding that it was possible to enhance immunogenicity by a single freeze-thaw cycle (freezing at -18.degree.) was unexpected. Although storage at -70.degree. and 25.degree. resulted in more variable responses, there was no clear trend that might be predictive for length of feasible storage time; in addn., immunogenicity was not altered from the time 0 control. However, not all emulsion formulations showed the stable storability according to this invention. Accordingly, the emulsions capable of withstanding freezing have been found to include Montanide ISA 25, 703, 719, and 720.

L29 ANSWER 3 OF 14 CAPLUS COPYRIGHT 2002 ACS

2001:359834 Document No. 134:365700 Improved method of immunization by separate administration of immunogen and immunostimulant. Gevas, Philip C.; **Michaeli, Dov; Grimes, Stephen** (Aphton Corporation, USA). PCT Int. Appl. WO 2001034192 A2 20010517, 20 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG,

SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US30778 20001108. PRIORITY: US 1999-PV164054 19991108.

AB A method for improving the immune response to a immunogen by sep. administering to a patient an immunogen compn. for sustained release comprising an epitope of the immunogen target, and a supplement comprising an adjuvant compd. for stimulating, potentiating or activating a strong immune response. The provided method potentially reduces local irritation at the sites of inoculation, i.m. or s.c.

L29 ANSWER 4 OF 14 CAPLUS COPYRIGHT 2002 ACS

2001:755699 Document No. 135:317452 Methods for the treatment of hormone-dependent tumors with immunogens against gonadotropin releasing hormone. **Grimes, Stephen;** Scibienski, Robert (Aphton Corporation, USA). U.S. US 6303123 B1 20011016, 24 pp., Cont.-in-part of U.S. 5,688,506. (English). CODEN: USXXAM. APPLICATION: US 1995-478546 19950607. PRIORITY: US 1994-188223 19940127.

AB Immunogenic compns. capable of generating an immune response in mammals against **GnRH** are disclosed. The immunogenic compns. are effective in methods of treating gonadotropin and gonadal steroid hormone dependent diseases and immunol. contraception of mammals.

L29 ANSWER 5 OF 14 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

2001:253026 Document No.: PREV200100253026. Immunogens against gonadotropin releasing hormone. **Grimes, Stephen (1);** Scibienski, Robert. (1) Davis, CA USA. ASSIGNEE: Aphton Corp., Woodland, CA, USA. Patent Info.: US 6132720 October 17, 2000. Official Gazette of the United States Patent and Trademark Office Patents, (Oct. 17, 2000) Vol. 1239, No. 3, pp. No Pagination. e-file. ISSN: 0098-1133. Language: English.

AB Immunogenic compositions capable of generating an immune response in mammals against **GnRH** are disclosed. The immunogenic compositions are effective in methods of treating gonadotropin and gonadal steroid hormone dependent diseases and immunological contraception of mammals.

L29 ANSWER 6 OF 14 MEDLINE DUPLICATE 1

2000400887 Document Number: 20399585. PubMed ID: 10945488. Anti-**GnRH** antibodies can induce castrate levels of testosterone in patients with advanced prostate cancer. Simms M S; Scholfield D P; Jacobs E; **Michaeli D;** Broome P; Humphreys J E; Bishop M C. (Department of Urology, City Hospital, Nottingham, UK.) BRITISH JOURNAL OF CANCER, (2000 Aug) 83 (4) 443-6. Journal code: 0370635. ISSN: 0007-0920. Pub. country: SCOTLAND: United Kingdom. Language: English.

AB D17DT consists of the **GnRH** decapeptide linked to diphtheria toxoid. The aim of this pilot study was to assess the tolerance of D17DT and the production of anti-**GnRH** antibodies from two doses, 30 and 100 microg, in patients with locally advanced prostate cancer. Twelve patients with histologically proven prostate cancer in whom hormonal therapy was indicated were recruited. Patients received either 30 or 100 microg given intramuscularly on three separate occasions over six weeks. Patients were followed up and blood was taken for estimation of serum testosterone, PSA and anti-**GnRH** antibody titre. Overall the drug was well tolerated. In 5 patients a significant reduction in serum testosterone and PSA was seen. Castrate levels of testosterone were achieved in 4 and maintained for up to 9 months. Patients with the highest antibody titre had the best response in terms of testosterone suppression. This study shows that it is possible to immunize a patient with prostate cancer against **GnRH** to induce castrate levels of testosterone. This state appears to be reversible. This novel form of immunotherapy may have advantages over conventional forms of hormonal therapy and further studies are warranted in order to try and increase the proportion of responders.

L29 ANSWER 7 OF 14 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
2000:405190 Document No.: PREV200000405190. Anti-**GnRH** antibodies can induce castrate levels of testosterone in patients with advanced prostate cancer. Simms, M. S. (1); Scholfield, D. P.; Jacobs, E.; **Michaeli, D.**; Broome, P.; Humphreys, J. E.; Bishop, M. C.. (1) Department of Urology, City Hospital, Hucknall Rd, Nottingham, NG51PB UK. European Journal of Cancer, (July, 2000) Vol. 36, No. Supplement 2, pp. 443-446. print. ISSN: 0959-8049. Language: English. Summary Language: English.

AB D17DT consists of the **GnRH** decapeptide linked to diphtheria toxoid. The aim of this pilot study was to assess the tolerance of D17DT and the production of anti-**GnRH** antibodies from two doses, 30 and 100 mug, in patients with locally advanced prostate cancer. Twelve patients with histologically proven prostate cancer in whom hormonal therapy was indicated were recruited. Patients received either 30 or 100 mug given intramuscularly on three separate occasions over six weeks. Patients were followed up and blood was taken for estimation of serum testosterone, PSA and anti-**GnRH** antibody titre. Overall the drug was well tolerated. In 5 patients a significant reduction in serum testosterone and PSA was seen. Castrate levels of testosterone were achieved in 4 and maintained for up to 9 months. Patients with the highest antibody titre had the best response in terms of testosterone suppression. This study shows that it is possible to immunize a patient with prostate cancer against **GnRH** to induce castrate levels of testosterone. This state appears to be reversible. This novel form of immunotherapy may have advantages over conventional forms of hormonal therapy and further studies are warranted in order to try and increase the proportion of responders.

L29 ANSWER 8 OF 14 MEDLINE DUPLICATE 2
1999314756 Document Number: 99314756. PubMed ID: 10408837. Anti-gonadotrophin releasing hormone antibodies inhibit the growth of MCF7 human breast cancer xenografts. Jacobs E; Watson S A; **Michaeli D** ; Ellis I O; Robertson J F. (Department of Surgery, University Hospital, Nottingham, UK.) BRITISH JOURNAL OF CANCER, (1999 May) 80 (3-4) 352-9. Journal code: 0370635. ISSN: 0007-0920. Pub. country: SCOTLAND: United Kingdom. Language: English.

AB The human breast cancer cell line (MCF7) was established as xenografts in intact female nude mice. Xenografts did not require oestrogen supplementation for growth, although oestrogen supplementation caused more rapid tumour growth. **GnRH** Pharmaccine is an immunogen composed of gonadotrophin releasing hormone (**GnRH**) linked to diphtheria toxoid. Anti-**GnRH** antibodies purified from the serum of rabbits immunized with **GnRH** Pharmaccine, were used to passively immunize nude mice. In mice treated with anti-**GnRH** antibodies, xenograft growth was significantly inhibited relative to controls (median times of 71 and 29 days respectively taken for tumours to attain a predetermined cross-sectional area of 200 mm2, $P < 0.001$). The inhibition of tumour growth achieved by anti-**GnRH** antibodies was not significantly different from that produced by the anti-oestrogen, tamoxifen (59 days). Ovarian/uterine weights were reduced by 61% ($P < 0.001$) in anti-**GnRH** antibody-treated animals compared with controls. Histologically there was underdevelopment and atrophy of the reproductive organs. Serum levels of both oestrogen and luteinizing hormone were reduced by treatment with anti-**GnRH** antibodies (to 24.9% and 53% respectively of levels in controls, both $P = 0.04$). It is postulated that one of the mechanisms by which anti-**GnRH** antibody treatment inhibits tumour growth is indirectly, by reducing serum oestrogen levels.

L29 ANSWER 9 OF 14 MEDLINE DUPLICATE 3
1999041226 Document Number: 99041226. PubMed ID: 9825853. Late luteal rescue in the baboon (Papio cynocephalus). Castracane V D; **Stevens V**; Knickerbocker J; Powell J; Randolph M; Gimpel T. (Department of

Obstetrics and Gynecology, Texas Tech University Health Sciences Center, Amarillo 79106, USA.. debbie@cortex.ama.ttuhsc.edu) . HUMAN REPRODUCTION UPDATE, (1998 Jul-Aug) 4 (4) 383-8. Ref: 12. Journal code: 9507614. ISSN: 1355-4786. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Numerous studies have used human chorionic gonadotrophin (HCG) administration to study the response of the primate ovary to gonadotrophin stimulation. These studies are generally performed in the luteal phase with very few studies of the follicular phase. We have studied the effect of both HCG and gonadotrophin releasing hormone (**GnRH**) agonist administered at the early follicular phase in normally cycling baboons (Papio cynocephalus). Five baboons were treated with increasing doses of HCG for 5 consecutive days starting on day 1 of the cycle and three untreated baboons served as controls. Follicular and luteal phase lengths were determined and serum samples were assayed for progesterone, oestradiol and 17alpha-OH progesterone. In a separate study, six baboons were treated with **GnRH** agonist (WY-40972) on days 2-6 of the cycle and saline-treated baboons served as controls (n = 5). Mean peak progesterone concentrations (+/- SE) during the treatment interval were 3.88+/-0.56 ng/ml in HCG-treated baboons compared to 0.19+/-0.07 ng/ml in controls ($P < 0.001$). A similar significant increase ($P < 0.001$) in serum 17alpha-OH progesterone concentrations was also observed (6.13+/-1.12 ng/ml versus 1.13+/-0.49 ng/ml). In association with the increase in luteal steroids there was also a significant prolongation of menstrual cycle length from 32.7+/-1.2 days in controls to 46.8+/-4.9 days in HCG-treated baboons ($P < 0.05$), which involved prolongation of the follicular phase (16.7+/-1.2 days to 29.0+/-4.6 days; $P < 0.05$) with no difference in luteal phase length or progesterone concentrations. In **GnRH** agonist-treated baboons, mean (+/- SE) cycle length was prolonged to 46.3+/-1.6 days and in saline-treated controls was 32.8+/-0.8 days ($P < 0.001$), again this was completely represented by the change in follicular phase length, from 13.4+/-0.7 days in controls to 27.2+/-2.1 days in agonist-treated baboons ($P < 0.001$). In contrast, there was no significant difference in luteal phase length between these two groups (19.4+/-0.7 versus 19.2+/-1.0 days). The prolongation of the follicular phase was accompanied by significant increases in both progesterone ($P < 0.01$) and oestradiol ($P < 0.01$) during **GnRH** agonist treatment above control concentrations. Luteal phase concentrations of these hormones were not different from controls. These results demonstrate the previously unreported finding that gonadotropin stimulation will rescue the corpus luteum in the next follicular phase.

L29 ANSWER 10 OF 14 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

1996:255655 Document No.: PREV199698811784. **GnRH** antibodies inhibit the growth of MCF-7 xenografts. Robertson, J. F. R. (1); Jacobs, E. (1); Watson, S. A. (1); **Michaeli, D.**. (1) Dep. Surg., City Hospital, Nottingham UK. Proceedings of the American Association for Cancer Research Annual Meeting, (1996) Vol. 37, No. 0, pp. 227. Meeting Info.: 87th Annual Meeting of the American Association for Cancer Research Washington, D.C., USA April 20-24, 1996 ISSN: 0197-016X. Language: English.

L29 ANSWER 11 OF 14 CAPLUS COPYRIGHT 2002 ACS

1995:867771 Document No. 123:254560 Immunogens against gonadotropin releasing hormone (**GnRH**). **Grimes, Stephen;** Scibienski, Robert (Aphton Corp., USA). PCT Int. Appl. WO 9520600 A1 19950803, 39 pp. DESIGNATED STATES: W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, JP, KG, KP, KR, KZ, LK, LR, LT, LV, MD, MG, MN, MX, NO, NZ, PL, RO, RU, SI, SK, TJ, TT, UA, UZ, VN; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1995-US1225 19950126. PRIORITY: US 1994-188223 19940127.

AB Immunogenic compns. capable of generating an immune response in mammals against **GnRH** are disclosed. The immunogenic compns. are effective in methods of treating gonadotropin and gonadal steroid hormone

dependent diseases and immunol. contraception of mammals. In example, four immunogenic peptides were synthesized, conjugated with diphtheria toxoid, and used as immunogen.

L29 ANSWER 12 OF 14 MEDLINE
2002555606 Document Number: 21757638. PubMed ID: 12345606. Anti-fertility vaccines: current status and implications for family planning programmes. Griffin P D; Jones W R; **Stevens V C**. Reprod Health Matters, (1994 May) (3) 108-13. Journal code: 9420826. ISSN: 0968-8080. Report No.: PIP-099696; POP-00232547. Pub. country: ENGLAND: United Kingdom. Language: English.

AB The basic principal of an anti-fertility vaccine is to use the body's own immune defense mechanisms to provide protection against unplanned pregnancies. The perceived advantages of such vaccines over currently available family planning methods are that they would not cause hormonal and metabolic disturbances, would not require daily pill-taking, would not present storage and disposal problems, would not require specialized insertion and removal procedures, would not depend upon the strict self-discipline demanded by natural family planning, would be naturally reversible, and would offer the man or woman personal confidentiality of use. A major objective of the World Health Organization Special Program's research is therefore to develop anti-fertility vaccines with a duration of effect of 12-18 months following a single injection or oral administration, thereby providing a suitable method for delaying a first birth, spacing births, and providing a reversible alternative to surgical sterilization after childbearing has been completed. The authors discuss anti-sperm and anti-egg vaccines, anti-**GnRH** and anti-FSH vaccines, anti-hCG vaccines, the current status of anti-hCG vaccine development, the acceptability of anti-fertility vaccines, and further development and testing in the areas of long-term safety, the predictability of duration of effect, reversal, oral administration versus injection, and anti-fertility vaccines and HIV/AIDS.

L29 ANSWER 13 OF 14 MEDLINE
92383517 Document Number: 92383517. PubMed ID: 1514029. Future perspectives for vaccine development. **Stevens V C**. (Department of Obstetrics and Gynecology, Ohio State University, Columbus 43210-1228.) SCANDINAVIAN JOURNAL OF IMMUNOLOGY. SUPPLEMENT, (1992) 11 137-43. Journal code: 7501626. ISSN: 0301-6323. Report No.: PIP-077824; POP-00218898. Pub. country: ENGLAND: United Kingdom. Language: English.

AB The successful development of an anti-fertility vaccine necessitates overcoming obstacles in eliciting an immune response to self species body constituents. The feasibility of accomplishing this task has been demonstrated for certain antigens described in this workshop; however, additional vaccine candidate antigens may yet be revealed from the application of recent advances in molecular biology. Improvements in vaccine design are likely to occur from discovery of more appropriate epitopes on targeting antigens, new carrier molecules for terminating immunological tolerance, expression of vaccine antigens in suitable live vectors, the co-immunization with more than one antigen, the use of safer and/or more effective adjuvants and vehicles, more efficient immunization by targeting antigens to specific lymphoid cells, and the development of superior vaccine delivery systems. Research directed to restricting the immune response to the genital tract and to intentionally reverse the effects of immunization will likely be pursued in the future. All of these areas need to be addressed if vaccines are to be developed that are not only safe and effective but also highly acceptable as birth control methods.
Reproductive hormone-based vaccines have targeted single molecules, sperm, and ovum antigens. Also, a peptide representing hormone-specific epitopes has been employed for vaccine development for the human chorionic gonadotropin (hCG) vaccine. Defining individual epitopes is needed because

few defined molecules can be acquired from natural sources to manufacture vaccine for millions of people, and recombinant DNA production of glycosylated molecules is expensive. Most research will be directed toward defining antigen-specific epitopes in follicle stimulating hormones (FSH), gonadotropin releasing hormones (**GnRH**), hcG, the sperm antigens, and ovum antigens. The first vaccines using recombinant fusion proteins have now emerged. They utilize T-cell and B-cell epitopes, as responses to both are needed to prevent infection. The immune response required for an antifertility vaccine requires overcoming a state of total T-cell tolerance and partial B-cell tolerance to render self antigens immunogenic to temporarily neutralize reproductive or eliminating hypersensitivity reactions elicited by T-cell activation. Currently approved vaccines are delivered by the injection of antigens dissolved in physiological saline or absorbed to aluminum hydroxide precipitates. Biodegradable microsphere systems for controlled antigen release hold out the promise of a sustained antibody response to a soluble antigen, as they employ synthetic polymers of polylactic acids to entrap immunogens and to release them gradually over time. The acceptability of antifertility vaccines hinges on clearly defining the duration of infertility. Any birth control method inducing long term infertility provides opportunities for ethical abuse with inadequate informed consent or by coercive governments, thus stringent adherence to high ethical standards accompany their use.

L29 ANSWER 14 OF 14 MEDLINE DUPLICATE 4

84235769 Document Number: 84235769. PubMed ID: 6329644. Levels of adrenal and gonadal hormones in rhesus monkeys during chronic hypokinesia. Goncharov N P; Tavadyan D S; Powell J E; **Stevens V C.** ENDOCRINOLOGY, (1984 Jul) 115 (1) 129-35. Journal code: 0375040. ISSN: 0013-7227. Pub. country: United States. Language: English.

AB The purpose of this study was to evaluate the effect of chronic immobilization on the hypophysial-adrenal and hypophysial-gonadal axes of adult male rhesus monkeys and the effect such manipulation has on the ability of these axes to respond to exogenous corticotropin, gonadotropin, and **GnRH** administration. A comparison was also made of the effects of immobilization on testosterone secretion at periods of low (April) and high (November) gonadal activity in this animal. Adult male rhesus monkeys were immobilized in a horizontal position for periods of up to 20 days during March/April. The function of the hypophysial-adrenal and hypophysial-gonadal axes was studied by monitoring plasma levels of cortisol, 17-hydroxylated precursors, 11 deoxycortisol, and testosterone during the period of restraint. Groups of immobilized and control animals also received iv injections of ACTH, FSH, and LH or LHRH on day 18 of the experiment. An additional group of animals was immobilized for 20 days, but did not receive exogenous hormone treatment. This group was used for comparison of seasonal differences in testosterone secretion with another group of animals subjected to the same treatment in November. During the first 3 h of immobilization, levels of cortisol, 17-hydroxylated precursors, and 11-deoxycortisol increased markedly from initial levels. Cortisol levels remained elevated for 3 days, whereas levels of the other three adrenal hormones declined to near-initial levels within 24 h. Testosterone levels declined steadily during the first 6 h of immobilization in males studied at a time of high testicular activity (November), while an increase during the first hour of restraint followed by a decline during the next 3 days were observed in males studied during a period of low testicular activity (April). Animals injected with ACTH on day 18 of immobilization had cortisol levels similar to those of control animals, but other groups of animals restrained for a similar period exhibited a lower level of plasma testosterone than controls after the injection of FSH and LH or LHRH. These data suggest that adaptation to stress results in a reduced demand for corticosteroid production and that the adrenals of chronically stressed animals are capable of responding to exogenous corticotropin, or alternatively, the immobilization imposed was stressful for only a limited time, and after a few days, animals no longer

reacted as in response to stress. Also, secretion of testosterone in male monkeys is markedly influenced by the functional state of the gonads at the time of stress initiation.

=>

---Logging off of STN---

=>
Executing the logoff script...

=> LOG Y

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	147.88	148.09

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-8.05	-8.05

STN INTERNATIONAL LOGOFF AT 10:15:50 ON 10 OCT 2002

77702

Delaval, Jan

From: Huynh, Phuong N.
Sent: Thursday, October 10, 2002 9:22 AM
To: Delaval, Jan
Subject: RE: 09/848,834

Jan,

Please search peptide (open & close) of SEQ ID NO: 1, 9-20 against commercial and interference databases.

Thanks,
Neon
Art unit 1644
Mail 9E12
Tel 308-4844

Jan Delaval
Reference Librarian
Biotechnology & Chemical Library
CM1 1E07 – 703-308-4498
jan.delaval@uspto.gov